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1626-

PATENT

Customer Number: 22,852

Attorney Docket No. 02481.1718.00

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Uwe HEINELT *et al.*

Application No.: 09/734,008 ✓

Filed: December 12, 2000

For: SUBSTITUTED
NORBORNYLAMINO
DERIVATIVES, PROCESSES
FOR THEIR PREPARATION,
THEIR USE AS
MEDICAMENTS OR
DIAGNOSTICS, AND A
MEDICAMENT COMPRISING
THEM

) Group Art Unit: 1626 ✓

) Examiner: E. Sackey

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

REQUEST FOR RECONSIDERATION UNDER 37 C.F.R. §1.111

In reply to the non-final Office Action of April 17, 2003, Applicants respectfully request, pursuant to 37 C.F.R. § 1.111, reconsideration in light of the following remarks.

I. Status of the Application and Claims

Claims 1-50 are pending in this application. The Office has rejected Claims 1-3, 25, and 26. The Office has objected to the remaining claims, 4-24 and 27-50, as being dependent upon a rejected base claim, but has indicated that they “would be allowable

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if rewritten in independent form including all of the limitations of the base claim and any intervening claims.” (Office Action at 6.)

II. Bondavalli Does Not Anticipate Applicants’ Claim 1

The Office has rejected Claim 1 under 35 U.S.C. § 102(b) as being anticipated by F. Bondavalli et al., “Synthesis and Pharmacological Activity of Derivatives of *Exo*-trimethylenenorbornane,” *Il Farmaco - Edizione Scientifica*, Vol. 34, No. 11 (Nov. 1979), pp. 945-51 (hereinafter referred to as “Bondavalli”). (Office Action at 3.) Applicants traverse the rejection.

A reference anticipates a claim “only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.” MPEP § 2131 (8th ed., Rev. 1, Feb. 2003) (emphasis added) (quoting *Verdegaal Bros. v. Union Oil Co. of Cal.*, 2 U.S.P.Q.2d (BNA) 1051, 1053 (Fed. Cir. 1987)). In the context of a claim covering a genus of chemical compounds, a prior art reference must disclose at least one species within that genus for the Office to properly reject the claim as anticipated. *Id.* § 2131.02 (citing *In re Slayter*, 125 U.S.P.Q. (BNA) 345, 347 (C.C.P.A. 1960)).

Applicants’ Claim 1 covers a genus of chemical compounds. Each of the compounds in that genus has as an element an “exo-configured nitrogen.” (Claim 1, lines 1, 3, as amended 8/7/02.) Therefore, in order for Bondavalli to anticipate Claim 1 it must disclose at least one compound within that claimed genus that includes this exo-configured-nitrogen element, along with each and every other element of one of the compounds of Claim 1. Bondavalli does not provide this teaching.

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The Office asserts that “Applicants claim a substituted norbornylamino compound of formula (I) and (Ia)” and that Bondavalli discloses a substituted norbornylamino compound “which is identical to the instantly claimed compound.” (Office Action at 3 (citing Bondavalli at 949 and compound (Vd) therein).) The Office does not explain the factual rationale for its ultimate finding of anticipation. But by citing compound (Vd), the Office implicitly asserts that compound (Vd) possesses every element required by Claim 1, including the exo-configured-nitrogen element. Analyzing Bondavalli shows, however, that the Office’s assertion is untrue.

Bondavalli “report[ed] the synthesis of *exo*-5,6-trimethylenenorbornan-2-endo-amine” and derivatives thereof, including compound (Vd). (Bondavalli at 946 (emphasis added).) Although the authors of Bondavalli could not confirm their compounds’ chemical structure using NMR, they were nevertheless confident that the amino group was in the *endo*-position. (*Id.*; see also *id.* at 949 (describing compound (Vd) as a “2-*endo*-amine[.]”).) Accordingly, because Bondavalli discloses compounds that are 2-*endo*-amines, they necessarily have an *endo*-configured nitrogen as opposed to the *exo*-configured nitrogen required by Applicants’ Claim 1. Therefore, Bondavalli fails to teach “each and every element as set forth in” Claim 1. On this basis, Applicants respectfully request that the Office reconsider Claim 1 and find that it is not anticipated under 35 U.S.C. § 102(b).

III. Bondavalli Does Not Render Any of Applicants’ Claims Obvious

The Office has rejected Claims 2, 3, 25, and 26 under 35 U.S.C. § 103(a) “as being unpatentable over” Bondavalli. (Office Action at 4-6.) Applicants traverse the rejection.

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The Office correctly cites *Graham v. John Deere Co. of Kansas City*, 148 U.S.P.Q. (BNA) 459 (1966), as setting forth the factual inquiries that one must perform to determine whether or not a claimed invention would have been obvious. (Office Action at 4.) As stated by the Office, one of the factual inquiries is determining the scope and content of the prior art. (*Id.*) Once that is performed, the prior art as a whole is compared with the claimed subject matter from the perspective of a person having ordinary skill in the art. (*Id.*) As part of this comparison, all claim elements (also referred to as claim limitations) “must be taught or suggested by the prior art” in order to establish a *prima facie* case of obviousness. MPEP § 2143.03 (citing *In re Royka*, 180 U.S.P.Q. (BNA) 580 (C.C.P.A. 1974)). Furthermore, “[i]t is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art.” *In re Wesslau*, 147 U.S.P.Q. (BNA) 391, 393 (C.C.P.A. 1965).

Cases decided after *Graham* provide additional guidance for analyzing the obviousness or nonobviousness of chemical inventions. For example, prior art that does not teach “any specific or significant utility for the disclosed compounds . . . is not sufficient to render structurally similar claims *prima facie* obvious because there is no motivation for one of ordinary skill in the art to make the reference compounds, much less any structurally related compounds.” MPEP § 2144.09 at 153 (citing *In re Sterniski*, 170 U.S.P.Q. (BNA) 343 (C.C.P.A. 1971)). And when a particular species in a broad disclosure is relied upon, there must be a showing that one of ordinary skill in the art would have been motivated to start with that species; it cannot be presumed

from the mere disclosure of the species that there is sufficient motivation to select and modify it. *See Yamanouchi Pharm. Co. v. Danbury Pharmacal, Inc.*, 56 U.S.P.Q.2d (BNA) 1641, 1645 (Fed. Cir. 2000) (“At the outset, Danbury did not show the required motivation for selecting example 44 as a lead compound.”).

The Office states that “Applicants claim a substituted norbornylamino compound of formula (I) and (Ia) having an *exo*-configured and an *endo*-fused five, six or seven membered ring. The substituents are as defined in claim 1.” (Office Action at 5.) But the Office does not mention the limitation of Claim 1 that the nitrogen be *exo*-configured.

With that omission, the Office cites compound (Vd) and states that “[t]he difference between the instant compounds and Bondavalli . . . is the homologous nature of the compounds.” (*Id.* (citing Bondavalli at 949 and compound (Vd) therein).) The Office cites no other species in addition to compound (Vd). The Office asserts that “the reference discloses that said compounds showed central nervous system depressant and anticonvulsant activity.” (*Id.* (citing Bondavalli at 945).) Not recognizing the structural differences between the respective nucleuses of the Bondavalli compounds and the compounds of Applicants’ invention, the Office then proceeds to conclude that “[o]ne of ordinary skill in the art would thus have been motivated to prepare compounds homologous to the compound of the reference with the expectation of obtaining additional compounds which are useful in the pharmaceutical industry.” (*Id.* at 6.)

The Office’s obviousness analysis is erroneous and requires reversal for at least three reasons. First, as demonstrated in the discussion of the anticipation rejection, the Bondavalli reference discloses a different class of compounds (*i.e.*, 2-*endo*-amines) than those the Applicants have invented (*i.e.*, compounds having *exo*-configured

nitrogen). Further, there is no suggestion in Bondavalli that changing the structure of the nucleus of a molecule from the endo-nitrogen configuration to the exo-nitrogen configuration would result in a molecule having equivalent functional activity. Thus, Bondavalli does not motivate one of ordinary skill in the art to synthesize the compounds that Applicants have invented. See MPEP § 2144.09 at 151 ("Isomers having the same empirical formula but different structures are not necessarily considered equivalent by chemists skilled in the art and therefore are not necessarily suggestive of each other.") (citing *Ex parte Mowry*, 91 U.S.P.Q. (BNA) 219 (Patent Office Bd. App. 1950)). This reason alone is sufficient to remove the rejection under § 103(a).

Second, the Office erroneously applied the general statement of utility in Bondavalli to the particular species, compound (Vd), relied upon to show structural obviousness. The section entitled "Summary" in Bondavalli states that "[s]ome amides showed CNS depressant and anticonvulsant activity, and an amine convulsant activity in mice." (Bondavalli at 945 (emphasis added).) The Office improperly relied on the statement regarding CNS and anti-convulsant activity that is only applicable to certain amides that were tested, *i.e.*, compounds (IVa), (IVd), and (IVg). (*Id.* at 950.) The compound relied upon by the Office, compound (Vd), is an amine that was not even tested at all for utility (*id.*), making that compound an inappropriate starting point for building a case that Applicants' compounds are obvious. MPEP § 2144.09 at 153 ("If the prior art does not teach any specific or significant utility for the disclosed compounds, then the prior art is not sufficient to render structurally similar claims *prima facie* obvious . . .") (citing *In re Stemniski*, 170 U.S.P.Q. (BNA) 343 (C.C.P.A. 1971));

cf. Yamanouchi Pharm., 56 U.S.P.Q.2d at 1645 (holding that insufficient motivation to select a particular compound as a starting point precluded establishment of a *prima facie* case of obviousness). This is a second and independently sufficient justification for removing the § 103 rejection.

Third, the Office did not note that Bondavalli teaches away from the selection and modification of amine compounds. The only amine tested in Bondavalli, compound (Vf), which was not mentioned in the Office Action, did not exhibit useful CNS or anticonvulsant activity. Indeed, it caused convulsions in mice, tending to suggest its unsuitability as a pharmaceutical product. (Bondavalli at 950.) Furthermore, compound (Vf) was “inactive in the other tests (anti-amphetamine, anti-reserpine, analgesic, anti-inflammatory and anti-sensitizing activities).” (*Id.*) Given the disclosed usefulness of the amides (IVa), (IVd), and (IVg) as CNS-acting agents and anticonvulsants, and the undesirable results associated with the amine (Vf), Bondavalli as a whole teaches away from amine compounds, including the compound (Vd) cited and relied upon by the Office. *See, e.g., In re Gurley*, 31 U.S.P.Q.2d (BNA) 1130, 1131 (Fed. Cir. 1994) (“[I]n general, a reference will teach away if it suggests that the line of development flowing from the reference’s disclosure is unlikely to be productive of the result sought by the applicant.”). In other words, when Bondavalli is considered as a whole, the motivation upon which the Office bases the rejection does not exist. The teaching away by Bondavalli is yet another independent basis for removing the § 103 rejection.

There is an additional reason why claims 25 and 26 are not obvious over Bondavalli. Claims 25 and 26 respectively recite “[a] method of treating ischemic states of the peripheral nervous system, comprising administering an effective amount of a

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compound of formula I or I a as claimed in Claim 1 or a pharmaceutically acceptable salt thereof” and “[a] method of treating ischemic states of the central nervous system, comprising administering an effective amount of a compound of formula I or I a as claimed in Claim 1 or a pharmaceutically acceptable salt thereof.” The Bondavalli reference describes, among other things, amide compounds showing “CNS depressant and anticonvulsant activity.” (Bondavalli at 945.) The Office has not shown how that activity possessed by certain compounds disclosed in Bondavalli teaches or suggests a method of treating ischemic states of the peripheral or central nervous system, comprising administering an effective amount of a compound of formula I or I a as recited in Claim 1.

When Claims 2, 3, 25, and 26 are properly construed and Bondavalli is properly evaluated, the compelled result is a holding of nonobviousness for the reasons set forth above. Therefore, Applicants respectfully request that the Office reconsider those claims and find them allowable.

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IV. Conclusion

In view of the foregoing remarks, Applicants respectfully request the reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any required fees to our deposit account 06-0916.

Respectfully submitted,

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Dated: July 14, 2003

By: _____



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